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NAPHTHAMIDE DERIVATIVES AND THEIR USE

Field of the invention:

This invention relates to the treatment of diseases in which serotonin and Substance P or Neurokinin A are implicated, for example, in the treatment of disorders or conditions such as hypertension, depression, generalized anxiety disorder, phobias, posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders, obesity, chemical dependencies, cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders, Parkinson's disease, endocrine disorders vasospasm, cerebellar ataxia, gastrointestinal tract disorders, negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, attention deficit hyperactivity disorder, chronic paroxysmal hemicrania and headache.

Background:

The mammalian neurokinins are peptide neurotransmitters found in the peripheral and central nervous systems. The three principal neurokinins are Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB). N-terminally extended forms of at least NKA are known. Three receptor types are known for the principal neurokinins. Based upon their relative selectivities for the neurokinins SP, NKA and NKB, the receptors are classified as neurokinin 1 (NK_1), neurokinin 2 (NK_2) and neurokinin 3 (NK_3) receptors, respectively. In the periphery, SP and NKA are localized in C-afferent sensory neurons, which neurons are characterized by non-myelinated nerve endings known as C-fibers, and are released by selective depolarization of these neurons, or selective stimulation of the C-fibers. C-Fibers are located in the airway epithelium, and the tachykinins are known to cause profound effects which clearly parallel many of the symptoms observed in asthmatics. The effects of release or introduction of tachykinins in mammalian airways include bronchoconstriction, increased microvascular permeability, vasodilation, increased mucus secretion and activation of mast cells. Neurokinin antagonists that interact with NK_1, NK_2 and NK_3 receptors, having different chemical structures have been described.

NK_1 activity is also implicated in depression and anxiety, mice with genetically altered NK_1 receptors have decreased anxiety related behavior (Santarelli, L., *et. al.*, Proc. Nat. Acad. Sci. (2001), 98, 1912) and NK_1 antagonists have been reported to be effective in an animal model of depression (Papp, M., *et. al.*, Behav. Brain Res. (2000), 115, 19).

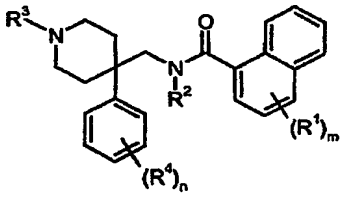
Serotonin Selective Reuptake Inhibitors (SSRIs) are widely used for the treatment of major depressive disorder (MDD) and are considered well-tolerated and easily administered. SSRIs, however, have a delayed onset of action, are associated with undesirable side effects, such sexual dysfunction, and are ineffective in perhaps 30% of patients (M. J. Gitlin, MJ, J. Clin. Psych., 55, 406-413, 1994).

Compounds with dual action as NK_1 antagonists and serotonin reuptake inhibitors may, therefore provide a new class of antidepressants. Indeed, compounds combining NK_1 antagonism and serotonin reuptake inhibition have been described (Ryckmans, T., *et. al.*, Bioorg. Med. Chem. Lett. (2002), 12, 261)

Description of the Invention:

This invention comprises novel naphthamide derivatives having dual NK_1 antagonist activity and SSRI activity, pharmaceutical compositions containing such compounds and methods of using such compounds to treat central nervous system (CNS) and other disorders.

Compounds of the present invention are those in accord with structural diagram I:



I

wherein:

R^1 independently at each occurrence is CN, CF_3, OCF_3, $OCHF_2$, halogen, C_{2-4}alkenyl, C_{2-4}alkynyl, R^a, R^b, SR^a, NR^aR^b, $CH_2NR^aR^b$, OR^a or CH_2OR^a, where R^a and R^b are independently at each occurrence hydrogen, C_{1-6}alkyl, $C(O)R^c$, $C(O)NHR^c$ or CO_2R^c, where R^c at each occurrence is C_{1-6}alkyl; or, R^a and R^b together are $(CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$, where G is oxygen or sulfur, j is 1, 2, 3 or 4, and k is 0, 1 or 2;

m is 1, 2 or 3 where at least one R^1 moiety is other than hydrogen;

R^2 and R^3 are independently hydrogen or C_{1-6}alkyl;

R^4 independently at each occurrence is hydrogen, CN, CF_3, OCF_3, $OCHF_2$, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, SR^a, NR^aR^b, $CH_2NR^aR^b$, OR^a or CH_2OR^a, where R^a and R^b are independently at each occurrence hydrogen, C_{1-6}alkyl, $C(O)R^c$, $C(O)NHR^c$ or CO_2R^c where R^c at each occurrence is C_{1-6}alkyl; or, R^a and R^b together are $(CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$ where G is oxygen or sulfur, j is 1, 2, 3 or 4, k is 0, 1 or 2, and

n is 0, 1, 2 or 3;

in vivo-hydrolysable precursors thereof, and pharmaceutically-acceptable salts thereof.

Particular compound of the invention are those wherein:

R^1 independently at each occurrence is CN, C_{1-6}alkyl or OR^c and m is 1, 2 or 3;

R^2 and R^3 are independently hydrogen or C_{1-6}alkyl, and

R^4 independently at each occurrence is halogen where n is 1 or 2;

in vivo-hydrolysable precursors thereof, and pharmaceutically-acceptable salts thereof.

More particular compound of the invention are those wherein:

R^1 independently at each occurrence is CN, ethyl or methoxy and m is 1, 2 or 3;

R^2 and R^3 are independently hydrogen or methyl, and

R^4 independently at each occurrence is halogen where n is 1 or 2;

in vivo-hydrolysable precursors thereof, and pharmaceutically-acceptable salts thereof.

Most particular compounds of the invention are those described herein

in vivo-hydrolysable precursors thereof, and pharmaceutically-acceptable salts thereof.

Pharmaceutically-acceptable salts of compounds in accord with structural diagram I include those made with inorganic or organic acids which afford a physiologically-acceptable anion, such as with, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, sulfamic, para-toluenesulfonic, acetic, citric, lactic, tartaric, malonic, fumaric, ethanesulfonic, benzenesulfonic, cyclohexylsulfamic, salicyclic and quinic acids.

In order to use a compound in accord with structural diagram I or an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof for the therapeutic treatment or prophylactic treatment of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore, another aspect the present invention is a pharmaceutical composition comprising a compound in accord with structural diagram I, an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof and a pharmaceutically-acceptable carrier.

Pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation or insufflation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous,

intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to herein.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.01 to 25 mg/kg body weight (and preferably of 0.1 to 5 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention. For example a tablet or capsule for oral administration may conveniently contain up to 250 mg (and typically 5 to 100 mg) of a compound in accord with structural diagram I or a pharmaceutically-acceptable salt thereof. In another example, for administration by inhalation, a compound in accord with structural diagram I or an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof may be administered in a daily dosage range of 5 to 100 mg, in a single dose or divided into two to four daily doses. In a further example, for administration by intravenous or intramuscular injection or infusion, a sterile solution or suspension containing up to 10% w/w (and typically 5% w/w) of a compound in accord with structural diagram I or an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof may be used.

Yet a further aspect of the present invention is a method of treating a disease condition wherein antagonism of NK_1 receptors in combination with SSRI activity is beneficial which method comprises administering to a warm-blooded animal an effective amount of a compound in accord with structural diagram I or an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof. The present invention also provides the use of a compound in accord with structural diagram I or an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof in the preparation of a medicament for use in a disease condition wherein antagonism of the NK_1 receptors and SSRI activity is beneficial.

The present invention also relates to a method for treating a disorder or condition selected from hypertension, depression in cancer patients, depression in Parkinson's patients,

postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, generalized anxiety disorder, agoraphobia, social phobia, simple phobias, posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, anorexia nervosa, bulimia nervosa, obesity, addictions to alcohol, cocaine, heroin, phenobarbital, nicotine or benzodiazepines; cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, dementia, amnestic disorders, age-related cognitive decline, dementia in Parkinson's disease, neuroleptic-induced parkinsonism, tardive dyskinesias, hyperprolactinaemia, vasospasm, cerebral vasculature vasospasm, cerebellar ataxia, gastrointestinal tract disorders, negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, attention deficit hyperactivity disorder, chronic paroxysmal hemicrania and headache associated with vascular disorders in a mammal, comprising administering an effective amount of a compound in accord with structural diagram I or a pharmaceutically-acceptable salt thereof effective in treating such disorder or condition and a pharmaceutically-acceptable carrier.

The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from hypertension, depression (e.g., depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, and post partum depression), generalized anxiety disorder, phobias (e.g., agoraphobia, social phobia and simple phobias), posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders (e.g., anorexia nervosa and bulimia nervosa), obesity, chemical dependencies (e.g., addictions to alcohol, cocaine, heroin, phenobarbital, nicotine and benzodiazepines), cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders (e.g., dementia, amnestic disorders, and age-related cognitive decline (ARCD)), Parkinson's diseases (e.g., dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias), endocrine disorders (e.g., hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract disorders (involving changes in motility and secretion), negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male

impotence, attention deficit hyperactivity disorder (ADHD), chronic paroxysmal hemicrania and headache (associated with vascular disorders) in a mammal, preferably a human, comprising an effective amount of a compound in accord with structural diagram I or a pharmaceutically-acceptable salt thereof effective in treating such disorder or condition and a pharmaceutically-acceptable carrier.

Compounds in accord with structural diagram I and their in vivo-hydrolysable precursors or a pharmaceutically-acceptable salts may be made by processes as described and exemplified herein and by processes similar thereto and by processes known in the chemical art. If not commercially available, starting materials for these processes may be made by procedures which are selected from the chemical art using techniques which are similar or analogous to the synthesis of known compounds.

Pharmaceutically-acceptable salts may be prepared from the corresponding acid in a conventional manner. Non-pharmaceutically-acceptable salts may be useful as intermediates and as such are another aspect of the present invention.

It is well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form or by synthesis from optically-active starting materials) and all optically active forms, enantiomers are compounds of this invention.

The following biological test methods, data and Examples serve to illustrate and further describe the invention.

The utility of a compound of the invention or an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof (hereinafter, collectively referred to as a "Compound") may be demonstrated by standard tests and clinical studies, including those disclosed in the publications described below.

Biological Assays:

SERT Binding Assay:

Frozen membrane preparations of a stably transfected HEK293 cell line expressing human 5-HTT receptors were purchased from Receptor Biology (PerkinElmer). Frozen alliquots were rapidly thawed, homogenized, and diluted in assay buffer (AB) containing 50 mM TRIS-HCL, 120 mM NaCl, 5 mM KCl and adjusted to pH 7.4 with NaOH. Final protein concentration was 40 µg/ml. Test compounds were evaluated in competition assays utlilizing [^{3}H]-Imipramine Hydrochloride purchased from NEN (PerkinElmer) as the radioligand. The stock radioligand was diluted with AB for a final concentration of approximately 2 nM. Kd for [^{3}H]-Imipramine Hydrochloride was determined to be 2.7 nM. The competition assays

were performed on 96-well assay plates – two drugs per plate. Ten serial dilutions (normally 1 μM to 38 pM final concentration) from stock 10 mM solutions of compounds prepared in DMSO. All serial dilutions were made using 20% DMSO. DMSO content in assay is less than 1%. Incubation mixtures were prepared in quadruplicate in 96-well plates (Costar). Final assay volumes per well were 10 μl compound/nonspecific/control (1% DMSO), 20 μl membranes, 20 μl [3H]-Imipramine Hydrochloride, and 150 μl AB. Specific binding was defined by using 10 μM Imipramine. The binding reaction was initiated by adding membranes immediately after adding the radioligand to wells containing buffer plus either test compound, nonspecific, or control. The assay plates were placed on a plate shaker and shaken for thirty minutes while the reactions reached equilibrium. The plates were then filtered through Beckman GF/B filters, presoaked in 6% PEI, using a Packard Filtermate 196. Filters were washed 5x with 0.2 ml ice-cold wash buffer (5 mM Tris HCl, pH 7.4.) After filters dried, 35 μl of Microscint20 (Packard) was added to each well. The plates were then counted on a Packard TopCount to determine CPM's per well. Ki values were determined for each test compound utilizing the graphic and analytical software package, GraphPad Prism.

NK_1 FLIPR Assay using Fluo-4 Dye:

FLIPR assays are performed with a device marketed by Molecular Devices, Inc., designed to precisely measure cellular fluorescence in a high throughput whole-cell assay. (Schroeder et. al., J. Biomolecular Screening, 1(2), p 75-80, 1996).

Compounds were evaluated for potency in blocking the response of U373 cells to the NK_1 receptor agonist Acetyl-[Arg^6, Sar^9, $Met(O_2)^{11}$]-Substance P (ASMSP) using a FLIPR instrument.

U373 cells were loaded with Fluo-4 dye (Molecular Probes) for 45 min at 37 °C and exposed to graded concentrations of compounds for 15 min at room temperature before being challenged with 10 nM – 12 nM ASMSP (an approximately EC_{80} concentration). Responses were measured as the peak relative fluorescence after agonist addition. pIC_{50}s were calculated from eleven-point concentration-response curves for each compound.

Reagents:

Cell culture medium:

Eagle's MEM with Earle's salts and l-glutamine (500 mL)	Cellgro 10-010-CV
Non-essential amino acids, 100 x (5 mL)	Cellgro 25-025-CI
Sodium pyruvate, 100 mM (5 mL)	Cellgro 25-000-CI
L-Glutamine, 200 mM (5 mL)	Cellgro 25-005-CI
FBS (50 mL)	Cellgro 35-010-CV

Cell harvesting reagents:

DPBS, 1x without Ca^{++} & Mg^{++}	Cellgro 21-031-CV
1x Trypsin –EDTA (0.5% Trypsin, 0.53% EDTA-4Na)	Cellgro 25-052-CI

Cell plating medium:

UltraCULTURE	BioWhittaker 12-725F
L-Glutamine, 200 mM (5 mL/500 mL)	Cellgro 25-005-CI

Working buffer:

10x Hank's balanced salt solution (100 mL/L)	Gibco 14065-056
HEPES buffer 1 M (15 mL/L, [final] 15 mM)	Cellgro 25-060-CI
Probenecid (0.71g dissolved in 6 mL 1 M NaOH for 1L, [final] 2.5 mM)	Sigma P-8761
DDH_20 to 1 L, adjust pH to 7.4 with NaOH	

Dye solution:

Fluo-4, AM dye, Molecular Probes F-14201. 50 µg lyophilized dye is dissolved in 23 µl DMSO plus 23 µL Pluronic F-127 (Molecular Probes P-3000). The 46 µL of solubilized fluo-4 dye is then added to 10 mL of working buffer solution to provide a working dye concentration of 5 µM. Each 10 mL of diluted dye is sufficient for a 384-well-plate of cells at 25 µL per well.

Agonist:

Acetyl-[Arg^6, Sar^9, $Met(O_2)^{11}$]-Substance P (ASMSP)

Stock solution of $3.33x10^{-2}$ M. Dissolve 100 mg in 3.05 mL DMSO and store in aliquots at 4 °C

Miscellaneous:

DMSO (to dissolve compounds and for tip wash)

Cell culture and plating procedures:

U373 cells were grown in cell culture medium described above (30 mL per T-150 flask) and harvested when confluent as follows. Medium was removed by aspiration and cells were washed with 12 mL DPBS, 1x without Ca^{++} and Mg^{++}. The DPBS was aspirated and replaced with 3 mL trypsin –EDTA. The cells plus trypsin/EDTA were incubated about 2 minutes at room temperature, until the cells detached from the flask. The harvesting reaction was quenched by addition of 9 mL culture medium and cells were resuspended by trituration. Cells were passaged at a transfer density of 1:4 every four days. For experiments, cells were counted, pelleted by centrifugation at 400 x g for 5 min and resuspended in cell plating medium at a density of 480,000 cells/mL. 25 µL of this cell suspension was added to each well of a black-walled 384-well plate (Falcon Microtest, 35 3962) using a Labsystems Multidrop 384 to give 12,000 cells per well. Plates were incubated at 37 °C overnight (minimum 15 h, maximum 23 h) before use.

Compound and agonist preparation:

Compounds were dissolved in DMSO at a concentration of 10 mM and 120 µL of these solutions were transferred to the first well (column 1) of each row of a 96-well, round-bottomed, polypropylene storage plate (Costar 3365). Compounds on two such plates were then serially diluted simultaneously in DMSO using a Biomek 2000. 4 µL of each dilution was transferred to a deep well plate (Beckman Coulter 267006) which had been prepared previously to contain 400 µL of freshly made working buffer in each well. Concentrations resulting from this procedure are shown in Table 1. The final compound concentrations in the assay span 11 points, between 10 µM and 0.1 nM, in half-log increments.

Table 1. Concentrations of compound and DMSO in various wells of a 96-well plate after serial dilution using Biomek 2000

Column number	Compound (Molarity)	DMSO (%)
1	1e-4	1
2	3e-5	1
3	1e-5	1
4	3e-6	1
5	1e-6	1

6	3e-7	1
7	1e-7	1
8	3e-8	1
9	1e-8	1
10	3e-9	1
11	1e-9	1
12	none	1

The contents of the deep wells were mixed, and 45 µL of each dilution were transferred - in duplicate - to a 384-well polypropylene compound loading plate (Fisher 12-565-507) so that the 384-well plate contained duplicates of each of the compounds from both 96-well plates in the concentrations shown in table 1. Columns 23 & 24 of the plate contain no compound and serve as controls. Wells A –N in columns 23 and 24 were loaded with agonist only and therefore represent the maximal response. Wells O – P in columns 23 and 24 were loaded with only buffer, no agonist, and therefore represent the minimum response.

An ASMSP agonist loading plate was made by taking stock concentration of ASMSP and diluting in working buffer to give a concentration of 3.3×10^{-8} M. 45 µL of this solution were transferred to all wells of a 384-well polypropylene agonist loading plate (Fisher 12-565-507) except wells O23, O24, P23 & P24 which contained buffer alone and served as unstimulated controls.

Dye Loading cells and adding compound:

For each 384-well assay plate of cells, 10 mL of diluted Fluo-4 dye was prepared as stated above in the methods/reagents section. First, each 384-well cell plate was washed once with working buffer on a CCS Packard plate washer. Any remaining post-wash buffer in the wells was removed by hand and 25 µL per well of Fluo-4 dye was added using a Labsystems Multidrop 384. The cell plate was returned to a 37 °C incubator for 45 min to allow the dye to permeate the cells. After 45 min of dye loading, the cell plates were washed twice with working buffer, leaving a 30 µL volume of buffer in each well. 5 µL of compound dilutions were transferred from the compound plate to the cell plate using a PlateMate Assay plates were incubated in the presence of compound for 15 min at room temperature in the dark, and then loaded onto FLIPR.

Recording responses in FLIPR:

After the 15 min compound pre-incubation, the plates were loaded onto the FLIPR instrument, 15 µL of ASMSP agonist was added and the cellular response to the agonist was recorded for 90 seconds. The response is measured as the peak relative fluorescence after agonist addition.

Data analysis:

Results contained in the *.stat* files generated by FLIPR were pasted into an Excel analysis template and, after outliers were excluded, IC_{50} values were calculated within the template using XLfit. Individual IC_{50} values were reported, along with pIC_{50}. When the two IC_{50}'s obtained for a compound differed by more than 3-fold that compound was assayed one or two more times to re-determine the value.

Compounds of the present invention exhibit a Ki in the range of 1 to 100 nM in the SERT assay and have an IC_{50} in the range 1 to100 nM in FLIPR assay

The invention is illustrated by, but not limited to, the following examples in which descriptions, where applicable and unless otherwise stated, the following terms, abbreviations and conditions are used:

aq., aqueous; atm, atmospheric pressure; BOC, 1,1-dimethylethoxycarbonyl; DCM, dichloromethane; DMF, N,N-dimethylformamide; DMSO, dimethyl sulfoxide; EtOH, ethanol; Et2O, diethyl ether; EtOAc, ethyl acetate; h, hour(s); HPLC, high pressure liquid chromatography; HOBT, 1-hydroxybenzotriazole; MeOH, methanol; min, minutes; MS, mass spectrum; NMR, nuclear magnetic resonance; psi, pounds per square inch; RT, room temperature; sat., saturated; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

Temperatures are given in degrees Celsius (°C); unless otherwise stated, operations were carried out at room or ambient temperature (18-25 °C).

Organic solutions were dried over anhydrous sodium or magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (4.5-30 mm Hg) with a bath temperature of up to 60 °C.

Chromatography means flash column chromatography on silica gel unless otherwise noted; solvent mixture compositions are given as volume percentages or volume ratios.

When given, NMR data is in the form of delta values for major diagnostic protons (given in parts per million (ppm) relative to tetramethylsilane as an internal standard) determined at 300 MHz.

Melting points are uncorrected.

Mass spectra (MS) were obtained using an automated system with atmospheric pressure chemical ionization (APCI) unless otherwise indicated. Masses corresponding to the major isotopic component, or the lowest mass for compounds with multiple masses with nearly equivalent abundance (isotope splitting), are reported.

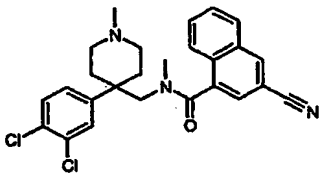
"Halogen" or "halo," as used herein means, fluoro, chloro, bromo and iodo.

Where noted that a final compound was converted to the citrate salt, the free base was dissolved in methanol, DCM, or acetonitrile, combined with citric acid (1.0 equivalents) in methanol, concentrated under reduced pressure and dried under vacuum (25-60 °C). When indicated that the salt was isolated by filtration from Et_2O, the citrate salt of the compound was stirred in Et_2O for 4-18 h, recovered by filtration, washed with Et_2O, and dried under vacuum (25-60 °C).

Examples:

Example 1: . 1-N-Methyl-4-(3,4-dichlorophenyl)-4-(3-(3-cyanonaphth-1-yl)-(3-oxo-2-N-methyl-2-azaprop-1-yl))piperidine.

The title compound of the following structure



was prepared as a citrate hemihydrate, as follows. A solution containing 3-cyano-1-naphthoyl chloride (as described in US patent 6,365,602) (141.2 mg, 0.655 mmol) and dry DCM (2 mL) was added in portions (0.25 mL) to a stirred solution containing 1-N-methyl-4-(3,4-dichlorophenyl)-4-(N-methylaminomethyl)piperidine (195.5 mg, 0.681 mmol), TEA (0.13 mL), and dry DCM (5 mL) at RT. After 72h, the mixture was partitioned between DCM and 1M aq. HOAc, the organic layer was removed, and the aqueous layer extracted with additional DCM (4X). The organic extracts were combined, washed (sat. aq. $NaHCO_3$), dried, filtered, and concentrated. The residue was purified by chromatography (2-10% MeOH-DCM w/0.5% aq. NH_3) and crystallization (DCM-hexane), converted to the citrate salt and isolated by filtration from Et_2O to give the title compound as a white powder. MS m/z 466 (M+H). Analysis for $C_{26}H_{27}Cl_2N_3O$. 1.0 $C_6H_8O_7$. 0.5 H_2O: Calculated: C, 57.58; H, 5.13; N, 6.29. Found: C, 57.42; H, 5.05; N, 6.24.

The requisite 1-N-methyl-4-(3,4-dichlorophenyl)-4-(N-methylaminomethyl)piperidine was prepared as follows:

a) 1-N-Methyl-4-(3,4-dichlorophenyl)-4-(N-methylaminomethyl)piperidine.

A solution containing 1-N-methyl-4-(3,4-dichlorophenyl)-4-(ethoxycarbonylaminomethyl) piperidine (2.14 g, 6.2 mmol) and dry THF (20 mL) was added to a $LiAlH_4$ and THF (40 mL) mixture at room temperature. The mixture was boiled under reflux for 1h, cooled to RT, and carefully treated with Na_2SO_4. 10 H_2O (in portions) until no further gas evolution was noted. The mixture was stirred at RT for 18h, filtered, and the solids washed with additional THF and toluene. The filtrates and washings were combined and concentrated to give the title compound as a light-yellow solid. The material was used without further purification. MS m/z 287 (M+H).

b) 1-Methyl-4-(3,4-dichlorophenyl)-4-(ethoxycarbonylaminomethyl)piperidine

A solution containing 1-N-methyl-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine (2.13 g, 7.80 mmol), TEA (1.36 mL), and dry DCM (15 mL) was cooled (ice bath), and a solution containing ethyl chloroformate (0.93 mL) and DCM (5 mL) was added dropwise over 20 min. After 40 min, cooling was removed and the solution was stirred at RT for an additional 3h. The reaction was diluted with additional DCM, washed with sat. aq. $NaHCO_3$ and brine, dried, filtered and concentrated. The residue was purified by chromatography (5-10% MeOH/DCM) to give the title compound as a viscous oil. MS m/z 345 (M+H).

c) 1-N-Methyl-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine

A mixture containing 1-N-methyl-4-(3,4-dichlorophenyl)-4-cyanopiperidine (2.1 g, 7.8 mmol), Raney Ni catalyst (1g of 50% aq. slurry), EtOH (50 mL), and ammonium hydroxide (25 mL) was placed under a hydrogen atmosphere (50 psi) and agitated (Parr apparatus) for 18 h. The mixture was filtered through diatomaceous earth and concentrated to give the title compound as a viscous oil that was used without further purification. MS m/z 273 (M+H).

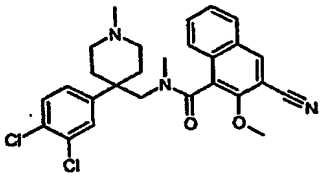
d) 1-N-Methyl-4-(3,4-dichlorophenyl)-4-cyanopiperidine.

According to procedures given in J. Het. Chem., 20, 771 (1983); ibid., 23, 73 (1986), a mixture containing 3,4-dichlorophenylacetonitrile (4.9 g, 26.44 mmol), N-methyl-bis-(2-chloroethyl)amine hydrochloride (5.1 g, 26.49 mmol), hexadecyltributylphosphonium bromide (0.72g, 1.43 mmol), and 50% aq. sodium hydroxide (30 mL) was heated at 100 °C for 1 hour, allowed to cool, treated with water (100 mL), and extracted with Et_2O (3X). The ether extracts were combined, washed with water (1X), and extracted with 1N aq. HCl (5X).

The acidic extracts were washed with Et_2O, neutralized with solid sodium carbonate, and extracted with Et_2O (2X). The ether extracts were dried, filtered and concentrated. The residual oil was purified by chromatography (0.5-2% MeOH/DCM) to give the title compound as a yellow oil. MS m/z 269 (M+H).

Example 2: 1-N-Methyl-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-(3-oxo-2-N-methyl-2-azaprop-1-yl))piperidine.

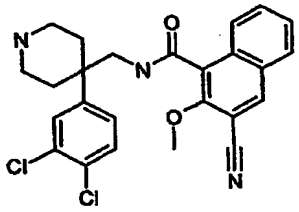
The title compound of the following structure



was prepared as a citrate hydrate, as follows. A solution containing 3-cyano-2-methoxy-1-naphthoyl chloride (described in international publication WO 00/20389) (151.9 mg, 0.618 mmol) and dry DCM (2 mL) was added in portions (0.25 mL) to a stirred solution containing 1-N-methyl-4-(3,4-dichlorophenyl)-4-(N-methylaminomethyl)piperidine (183.3 mg, 0.638 mmol), TEA (0.12 mL), and dry DCM (5 mL) at RT. After 72h, the mixture was partitioned between DCM and 1M aq. HOAc, the organic layer was removed, and the aqueous layer extracted with additional DCM (4X). The organic extracts were combined, washed (sat. aq. $NaHCO_3$), dried, filtered, and concentrated. The residue was purified by chromatography (2-10% MeOH-DCM w/0.5% aq. NH_3), converted to the citrate salt and isolated by filtration from Et_2O to give the title compound (white powder) as a mixture of (E) and (Z) amides. MS m/z 496 (M+H). Analysis for $C_{27}H_{27}Cl_2N_3O_2$. 1.0 $C_6H_8O_7$. 1.0 H_2O: Calculated: C, 56.10; H, 5.28; N, 5.95. Found: C, 56.44; H, 5.10; N, 5.98.

Example 3: 4-(3,4-Dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

The title compound of the following structure



was prepared as a citrate, as follows. A solution containing 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine (329 mg, 0.579 mmol) and DCM (5 mL) was stirred at room temperature and TFA (5 mL) was slowly added. After 18 h, the solution was concentrated, and the residue partitioned between DCM and sat. aq. $NaHCO_3$. The organic layer was removed and the basic aqueous layer was extracted with additional DCM (2X). The organic extracts were combined, dried, filtered, and concentrated. The residue was purified by chromatography (0-5% MeOH/DCM w/0.5% aq. NH_3) and converted to the citrate salt to give the title compound as a white powder. MS m/z 468 (M+H).

The requisite 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine was prepared as follows:

a) 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl) piperidine.

To a stirred solution containing 1-N-BOC-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine (260.8 mg, 0.726 mmol), 3-cyano-2-methoxy-1-naphthoic acid (164.6 mg, 0.724 mmol), HOBT hydrate (290 mg, 1.89 mmol), N-methylmorpholine (0.17 mL), and DCM (15 mL) was added 1-(3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (215.5 mg, 1.12 mmol). After 72h, the mixture was diluted with 30% hexane/EtOAc, washed successively with water (2X), 0.1 N aq. HCl (2X), sat. aq. $NaHCO_3$, dried, filtered, and concentrated. The residue was purified by chromatography (0-1% MeOH/DCM) to give the title compound as a white, foamy solid. MS m/z 468 .

b) 1-N-BOC-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine

A mixture containing 1-N-BOC-4-(3,4-dichlorophenyl)-4-cyanopiperidine (5.25 g, 14.78 mmol), Raney Ni catalyst (5g of 50% aq. slurry), EtOH (175 mL), and ammonium hydroxide (88 mL) was placed under a hydrogen atmosphere (50 psi) and agitated (Parr apparatus) for 18 h. The mixture was filtered through diatomaceous earth, concentrated, and purified by chromatography (0-5% MeOH/DCM) to give the title compound as an off-white solid. MS m/z 344 (M+1-CH_3). 1H NMR ($CDCl_3$) δ 7.44 (d, 1H), 7.38 (d, 1H), 7.15 (m, 1H), 3.7 (br d, 2H), 3.07 (m, 2H), 2.76 (s, 2H), 2.08 (br d, 2H), 1.71 (m, 2H), 1.44 (s, 9H).

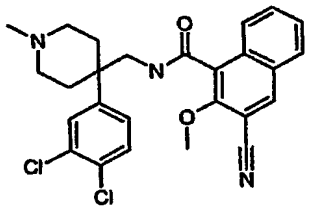
c) 1-N-BOC-4-(3,4-dichlorophenyl)-4-cyanopiperidine

A solution containing bis(2-chloroethyl)-N-BOC amine (described in US Patent 5,661,163) (8.15 g, 33.67 mmol), 3,4-dichlorophenylacetonitrile (5.05 g, 27.17 mmol), and DMSO (50 mL) was stirred at RT and solid cesium carbonate (17.6 g, 54.02 mmol) was

added (in portions) over 10 minutes. After 20 h, additional cesium carbonate (1.7 g,) was added, and the mixture stirred for an additional 72 h. The mixture was partitioned between water and EtOAc, the aqueous layer was removed, and the organic layer washed successively with additional water, 0.1M aq. HCl (2X), sat. aq. $NaHCO_3$, and brine. The organic layer was dried, filtered, concentrated, and the residue triturated (3:1 hexane/ethyl acetate) to give the title compound as an off-white solid, m.p. 142-145 °C. MS m/z 255 . 1H NMR ($CDCl_3$) δ 7.55 (d, 1H), 7.49 (d, 1H), 7.32 (m, 1H), 4.3 (br d, 2H), 3.18 (br t, 2H), 2.07 (d, 2H), 1.89 (m, 2H), 1.48 (s, 9H).

Example 4: 1-N-Methyl-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

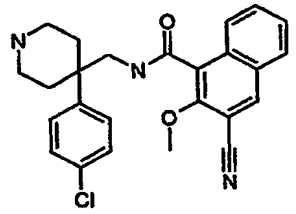
The title compound of the following structure



was prepared as a citrate, as follows. A solution containing 4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl) piperidine (103 mg, 0.22 mmol), formic acid (0.25 mL), and 37% aq. formaldehyde (2 mL) was heated at 100 °C. for 18h, then cooled and concentrated. The residue was partitioned between DCM and sat. aq. $NaHCO_3$ and the organic layer was removed. The basic aqueous layer was extracted with additional DCM (2X), and the combined organic extracts were dried, filtered, and concentrated. The residue was purified by chromatography (Chromatotron - silica rotor) (5% MeOH/DCM w/0.5% aq. NH_3) and converted to the citrate salt to give the title compound as a white powder. MS m/z 482 (M+H).

Example 5: 4-(4-Chlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

The title compound of the following structure



was prepared as a citrate, as follows. In the same manner as Example 3, but using 1-N-BOC-4-(4-chlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine (350 mg, 0.655 mmol), the citrate salt was isolated by filtration from Et_2O to give the title compound as a white powder. MS m/z 434 (M+H).

The requisite 1-N-BOC-4-(4-chlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine was prepared as follows:

a) 1-N-BOC-4-(4-chlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

In the same manner as Example 3a, but using 1-N-BOC-4-aminomethyl-4-(4-chlorophenyl) piperidine (244 mg, 0.75 mmol), 3-cyano-2-methoxy-1-naphthoic acid (170 mg, 0.748 mmol), HOBT hydrate (281 mg, 1.83 mmol), N-methylmorpholine (0.165 mL), 1-(3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (240 mg, 1.25 mmol), and DCM (10 mL), the title compound was obtained as a foamy solid. MS m/z 434 .

b) 1-N-BOC-4-aminomethyl-4-(4-chlorophenyl) piperidine.

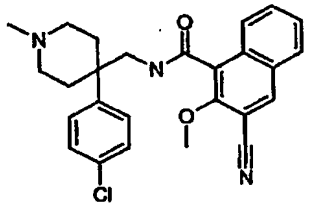
In the same manner as Example 3b, but using 1-N-BOC-4-(4-chlorophenyl)-4-cyanopiperidine (1.05 g, 3.26 mmol), Raney Ni catalyst (1.4 g of 50% aq. slurry), EtOH (50 mL), and ammonium hydroxide (25 mL), the title compound was obtained as a viscous oil. MS m/z 310 (M+H-Me).

c) 1-N-BOC-4-(4-chlorophenyl)-4-cyanopiperidine.

A solution containing bis(2-chloroethyl)-N-BOC amine (3.72 g, 15.38 mmol), 4-chlorobenzyl cyanide (2.10 g, 13.88 mmol), and anhydrous DMF (15 mL) was stirred and NaH (60% dispersion in mineral oil) (1.6 g, 40 mmol) was added in portions over 1h. The mixture was heated at 60-65 °C. for 1h, stirred at RT for 72h, then was poured into ice/water and extracted with EtOAc (2X). The organic extracts were washed (water and brine), dried, filtered, and concentrated. The residue was purified by chromatography (8:1:1 hexane/DCM/EtOAc) to give the title compound as a yellow solid. MS m/z 221 .

Example 6: 1-N-Methyl-4-(4-chlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

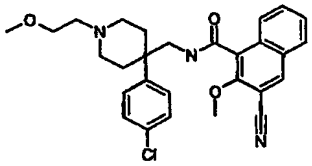
The title compound of the following structure



was prepared as a citrate, as follows. In the same manner as Example 4, but using 4-(4-chlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine (71.5 mg, 0.165 mmol), the citrate salt was isolated by filtration from Et_2O to give the title compound as a white powder. MS m/z 448 (M+H).

Example 7: 1-N-(2-Methoxyethyl)-4-(4-chlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl) piperidine.

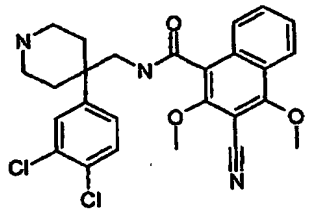
The title compound of the following structure



was prepared as a citrate, as follows. A solution containing 4-(4-chlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl) piperidine (38.5 mg, 0.089 mmol), 2-bromoethyl methyl ether (55.5 mg, 0.40 mmol), TEA (0.075 mL), and DMF (0.5 mL) was heated (microwave) at 60 °C. for 1.25 h, stirred at RT overnight, diluted with EtOAc, then washed successively with water (2X) and sat. aq. $NaHCO_3$. The organic phase was dried, filtered, and concentrated. The residue was purified by chromatography (2-5% MeOH/DCM w/ 0.5% aq. NH_3), converted to the citrate salt, and isolated by filtration from Et_2O to give the title compound as a white powder. MS m/z 492 (M+H).

Example 8: 4-(3,4-Dichlorophenyl)-4-(3-(3-cyano-2,4-dimethoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

The title compound of the following structure



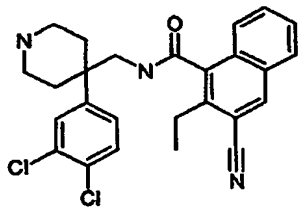
was prepared as a citrate, as follows. In the same manner as Example 3, but using 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2,4-dimethoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine (801 mg, 1.34 mmol), TFA (25 mL), and DCM (25 mL), the citrate salt of the title compound was obtained as a white, foamy solid. MS m/z 498 (M+H).

The requisite 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2,4-dimethoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine was prepared as follows:
1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2,4-dimethoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

A solution containing 3-cyano-2,4-dimethoxy-1-naphthoyl chloride (described in international publication WO 00/20389) (408.3 mg, 1.48 mmol) and dry DCM (2.5 mL) was added in portions (0.25 mL) to a stirred, cooled (ice bath) solution containing 1-N-BOC-4-(3,4-dichlorophenyl)-4-aminomethyl)piperidine (537 mg, 1.49 mmol), TEA (0.42 mL), and dry DCM (20 mL). After 1h, the reaction was warmed to RT, stirred an additional 1.5h, then concentrated. The residue was partitioned between water and EtOAc and the organic phase was removed and washed successively with 0.1N aq. HCl (2X), water, sat. aq. $NaHCO_3$ (2X), and brine. The organic phase was dried, filtered, concentrated, and the residue purified by chromatography (0-1% MeOH/DCM) to give the title compound as an off-white, foamy solid. MS m/z 498 .

Example 9: 4-(3,4-Dichlorophenyl)-4-(3-(3-cyano-2-ethylnaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

The title compound of the following structure



was prepared as a citrate, as follows. In the same manner as Example 3, but using 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-ethylnaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine (166.8 mg, 0.294 mmol), the citrate salt was isolated by filtration from Et_2O to give the title compound as a white powder. MS m/z 466 (M+H).

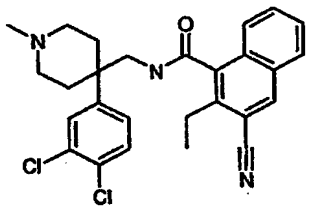
The requisite 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-ethylnaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine was prepared as follows:

1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-ethylnaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

In the same manner as Example 3a, but using 1-N-BOC-4-aminomethyl-4-(3,4-dichlorophenyl) piperidine (375 mg, 1.04 mmol), 3-cyano-2-ethyl-1-naphthoic acid (described in international publication WO 00/20389, (233 mg, 1.04 mmol), HOBT hydrate (399 mg, 2.6 mmol), N-methylmorpholine (0.23 mL), 1-(3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (330 mg, 1.72 mmol), and DCM (10 mL), the title compound was obtained as a foamy solid. MS m/z 466 .

Example 10: 1-N-Methyl-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-ethylnaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine.

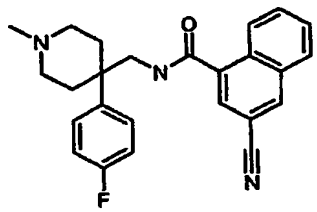
The title compound of the following structure



was prepared as a citrate, as follows. In the same manner as Example 4, but using 4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-ethylnaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine (69 mg, 0.148 mmol), the citrate salt was isolated by filtration from Et_2O to give the title compound as a white powder. MS m/z 480 (M+H).

Example 11: 1-N-Methyl-4-(4-fluorophenyl)-4-(3-(3-cyanonaphth-1-yl)-(3-oxo-2-azaprop-1-yl))piperidine.

The title compound of the following structure



was prepared as a citrate salt as follows. To a solution containing 3-cyano-1-naphthoic acid (0.435 g, 2.21 mmol), 1-N-methyl-4-(4-fluorophenyl)-4-(aminomethyl)piperidine (0.539 g, 2.43 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.676 g, 3.53 mmol) and 1-hydroxybenzotriazole (0.600 g, 4.44 mmol) in DCM (20 mL) was added TEA (0.92 mL, 6.60 mmol). The solution was stirred at room temperature overnight. The mixture was partitioned between DCM and saturated $NaHCO_3$, the organic layer was removed, and the aqueous layer extracted with DCM (2x). The organic extracts were combined, dried, filtered, and concentrated. The residue was purified by chromatography (1-5% MeOH-DCM w/1% aq. NH_3) to give the title compound as a white solid (0.7 g, 79% yield). MS m/z 402.50 (M+H). The citrate salt was obtained by standard procedure.

The requisite 1-N-methyl-4-(4-fluorophenyl)-4-(aminomethyl)piperidine was prepared as follows:

a) 1-N-Methyl-4-(4-fluorophenyl)-4-cyanopiperidine

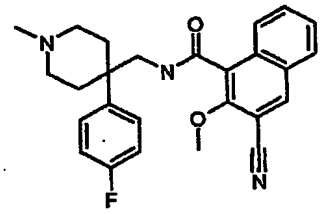
To a solution containing mechlorethamine hydrochloride (1.923 g, 9.99 mmol) and 4-fluorophenyl acetonitrile (1.35 g, 9.99 mmol) in DMF (30 mL) was added sodium hydride (1.6 g, 40 mmol) slowly at 0 °C. The resulting suspension was stirred and heated at 60 °C for 24 hrs. The reaction mixture was quenched with ice water, extracted with EtOAc (3x). The organic extracts were combined, washed with saturated NaCl (3x), dried, filtered, and concentrated. The residue was purified by chromatography (2-5% MeOH-DCM) to give the title compound as a yellow oil (1.788 g, 82% yield). MS m/z 219.38 (M+H).

b) 1-N-Methyl-4-(4-fluorophenyl)-4-(aminomethyl)piperidine

To a solution of 1-N-methyl-4-(4-fluorophenyl)-4-cyanopiperidine (1.788 g, 8.20 mmol) in dry THF (25 mL) was added LAH (1M in THF, 25mL, 24.6 mmol). The solution was stirred at room temperature overnight. The reaction was quenched by adding water (2.5 mL), followed by 15% NaOH (2.5 mL) and water (2.5 mL). The mixture was then filtered through diatomaceous earth, washed with EtOAc, dried, filtered, and concentrated to give the title compound as a yellow oil (1.619 g, 89% yield). MS m/z 223.45 (M+H).

Example 12: 1-N-Methyl-4-(4-fluorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-(3-oxo-2-azaprop-1-yl))piperidine.

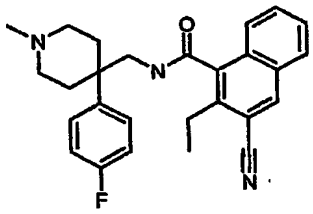
The title compound of the following structure



was prepared as a citrate salt in the same manner as Example 11, but using 3-cyano-2-methoxy-1-naphthoic acid (100 mg, 0.44 mmol), 1-N-methyl-4-(4-fluorophenyl)-4-(aminomethyl)piperidine (107 mg, 0.48 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (135 mg, 0.704 mmol), 1-hydroxybenzotriazole (119 mg, 0.88 mmol), DCM (5 mL), and TEA (0.184 mL, 1.32 mmol), the title compound was obtained as a white solid. 74% yield, MS m/z 432.46 (M+H).

Example 13: 1-N-Methyl-4-(4-fluorophenyl)-4-(3-(3-cyano-2-ethylnaphth-1-yl)-(3-oxo-2-azaprop-1-yl))piperidine.

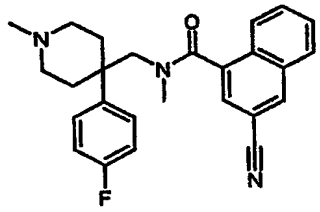
The title compound of the following structure



was prepared as a citrate salt as follows. To a solution containing 1-N-methyl-4-(4-fluorophenyl)-4-(aminomethyl)piperidine (98 mg, 0.441 mmol) and TEA (0.13 mL, 0.933 mmol) in DCM (5 mL) was added 3-cyano-2-ethyl-1-naphthoyl chloride (108 mg, 0.443 mmol) in DCM (1 mL) at 0 °C. The solution was stirred at 0 °C for 30 min and room temperature overnight. The mixture was partitioned between DCM and saturated $NaHCO_3$, the organic layer was removed, and the aqueous layer extracted with DCM (2x). The organic extracts were combined, dried, filtered, and concentrated. The residue was purified by chromatography (1-5% MeOH-DCM w/1% aq. NH_3) to give the title compound as a light yellow solid (156 mg, 82% yield). MS m/z 430.51 (M+H). The citrate salt was obtained by standard procedure.

Example 14: 1-N-Methyl-4-(4-fluorophenyl)-4-(3-(3-cyanonaphth-1-yl)-(3-oxo-2-N-methyl-2-azaprop-1-yl))piperidine.

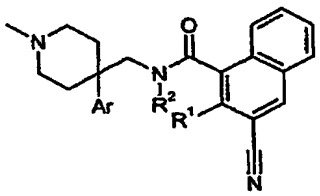
The title compound of the following structure

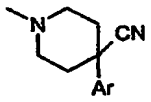


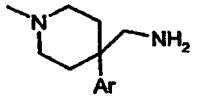
was prepared as a citrate salt as follows. To a solution of 1-N-methyl-4-(4-fluorophenyl)-4-(3-(3-cyanonaphth-1-yl)-(3-oxo-2-azaprop-1-yl))piperidine (366 mg, 0.912 mmol) in dry DMF (9 mL) was added NaH (44 mg, 1.1 mmol). The mixture was stirred at room temperature for 30 min and cooled to 0 °C. Methyl iodide (0.085 mL, 1.36 mmol) was added and the mixture was stirred at 0 °C for 30 min, room temperature overnight. The mixture was partitioned between EtOAc and water, the organic layer was removed, and the aqueous layer extracted with EtOAc (2x). The organic extracts were combined, washed with saturated NaCl (3x), dried, filtered, and concentrated. The residue was purified by chromatography (1-5% MeOH-DCM w/1% aq. NH_3) to give the title compound as a white solid (164 mg, 43% yield). MS m/z 416.54 (M+H). The citrate salt was obtained by standard procedure.

Example 11-34

Via reaction procedures similar to those given in Example 11-14 but with replacement of 4-fluorophenyl acetonitrile with an appropriately substituted phenyl acetonitrile, compounds of Examples 15 through 34 and intermediates listed in Table 2 were obtained.







Example #	Intermediate (a)	Intermediate (b)

Table 2

Example #	Ar	R^1	R^2	Yield (%)	MS m/z (M+H)
11	4-fluorophenyl	H	H	79	402.50
11 (a)	4-fluorophenyl			82	219.38
11 (b)	4-fluorophenyl			89	223.45
12	4-fluorophenyl	OMe	H	74	432.46
13	4-fluorophenyl	Et	H	82	430.51
14	4-fluorophenyl	H	Me	43	416.54
15	3,4-difluorophenyl	H	H	81	420.52
15 (a)	3,4-difluorophenyl			77	237.41
15 (b)	3,4-difluorophenyl			92	241.45
16	3,4-difluorophenyl	OMe	H	74	450.46
17	3,4-difluorophenyl	Et	H	44	448.51
18	3,4-difluorophenyl	H	Me	50	434.44
19	4-methoxyphenyl	H	H	78	414.53
19 (a)	4-methoxyphenyl			100	231.46
19 (b)	4-methoxyphenyl			93	235.49
20	4-methoxyphenyl	OMe	H	77	444.50
21	4-methoxyphenyl	Et	H	31	442.54
22	4-methoxyphenyl	H	Me	37	428.54
23	3,4-dimethoxyphenyl	H	H	67	444.52
23 (a)	3,4-dimethoxyphenyl			92	261.49
23 (b)	3,4-dimethoxyphenyl			86	265.52
24	3,4-dimethoxyphenyl	OMe	H	76	474.49
25	3,4-dimethoxyphenyl	Et	H	23	472.54
26	3,4-dimethoxyphenyl	H	Me	47	458.53
27	3,4-methylenedioxyphenyl	H	H	83	428.51
27 (a)	3,4-methylenedioxyphenyl			88	245.44
27 (b)	3,4-methylenedioxyphenyl			90	249.46
28	3,4-methylenedioxyphenyl	OMe	H	83	458.48
29	3,4-methylenedioxyphenyl	Et	H	62	456.40
30	3,4-methylenedioxyphenyl	H	Me	21	442.40

31	4-difluoromethoxyphenyl	H	H	74	450.53
31 (a)	4-difluoromethoxyphenyl			81	267.43
31 (b)	4-difluoromethoxyphenyl			62	271.48
32	4-difluoromethoxyphenyl	OMe	H	72	480.51
33	4-difluoromethoxyphenyl	Et	H	39	478.54
34	4-difluoromethoxyphenyl	H	Me	38	464.48

Example 35:

Following conventional procedures well known in the pharmaceutical art, the following representative pharmaceutical dosage forms containing a compound in accord with structural diagram I may be prepared:

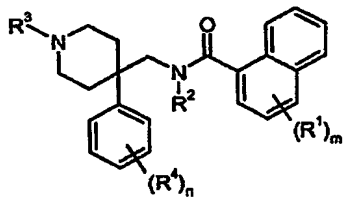
Tablet	mg/tablet
Compound in accord with structural diagram I	50.0
Mannitol, USP	223.75
Croscarmellose sodium	60
Maize starch	15
Hydroxypropylmethylcellulose (HPMC), USP	2.25
Magnesium stearate	3.0

Capsule	mg/capsule
Compound in accord with structural diagram I	10.0
Mannitol, USP	488.5
Croscarmellose sodium	15
Magnesium stearate	1.5

The pharmaceutical dosage form is administered to a patient in need thereof at a frequency depending on the patient and the precise disease condition being treated.

Claims:

1. A compound in accord with structural diagram I:



I

wherein:

R^1 independently at each occurrence is CN, CF_3, OCF_3, $OCHF_2$, halogen, C_{2-4}alkenyl, C_{2-4}alkynyl, R^a, R^b, SR^a, NR^aR^b, $CH_2NR^aR^b$, OR^a or CH_2OR^a, where R^a and R^b are independently at each occurrence hydrogen, C_{1-6}alkyl, $C(O)R^c$, $C(O)NHR^c$ or CO_2R^c, where R^c at each occurrence is C_{1-6}alkyl; or, R^a and R^b together are $(CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$, where G is oxygen or sulfur, j is 1, 2, 3 or 4, and k is 0, 1 or 2;

m is 1, 2 or 3 where at least one R^1 moiety is other than hydrogen;

R^2 and R^3 are independently hydrogen or C_{1-6}alkyl;

R^4 independently at each occurrence is hydrogen, CN, CF_3, OCF_3, $OCHF_2$, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, SR^a, NR^aR^b, $CH_2NR^aR^b$, OR^a or CH_2OR^a, where R^a and R^b are independently at each occurrence hydrogen, C_{1-6}alkyl, $C(O)R^c$, $C(O)NHR^c$ or CO_2R^c where R^c at each occurrence is C_{1-6}alkyl; or, R^a and R^b together are $(CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$ where G is oxygen or sulfur, j is 1, 2, 3 or 4, k is 0, 1 or 2, and

n is 0, 1, 2 or 3;

in vivo-hydrolysable precursors thereof, and pharmaceutically-acceptable salts thereof.

2. A compound according to Claim 1, wherein:

R^1 independently at each occurrence is CN, C_{1-6}alkyl or OR^c and m is 1, 2 or 3;

R^2 and R^3 are independently hydrogen or C_{1-6}alkyl, and

R^4 independently at each occurrence is halogen where n is 1 or 2;

in vivo-hydrolysable precursors thereof, and pharmaceutically-acceptable salts thereof.

3. A compound according to Claim 1, wherein:

R^1 independently at each occurrence is CN, ethyl or methoxy and m is 1, 2 or 3;

R^2 and R^3 are independently hydrogen or methyl, and

R^4 independently at each occurrence is halogen where n is 1 or 2;
in vivo-hydrolysable precursors thereof, and pharmaceutically-acceptable salts thereof.

4. A pharmaceutically-acceptable salts of a compound according to Claim 1 made with an inorganic or organic acid which affords a physiologically-acceptable anion.

5. A pharmaceutically-acceptable salts of a compound according to Claim 5, wherein said inorganic or organic acid is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, sulfamic, para-toluenesulfonic, acetic, citric, lactic, tartaric, malonic, fumaric, ethanesulfonic, benzenesulfonic, cyclohexylsulfamic, salicyclic and quinic acids.

6. A pharmaceutical composition comprising a compound according to Claim 1, an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof and a pharmaceutically-acceptable carrier.

7. A method of treating a disease condition wherein antagonism of NK_1 receptors in combination with SSRI activity is beneficial which method comprises administering to a warm-blooded animal an effective amount of a compound according to Claim 1 or an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof.

8. The use of a compound according to Claim 1 or an in vivo-hydrolysable precursor or a pharmaceutically-acceptable salt thereof in the preparation of a medicament for use in a disease condition wherein antagonism of the NK_1 receptors and SSRI activity is beneficial.

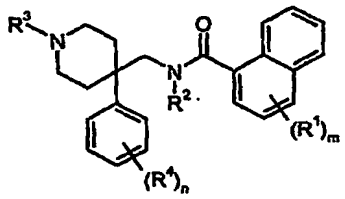
9. A method for treating a disorder or condition selected from hypertension, depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, generalized anxiety disorder, agoraphobia, social phobia, simple phobias, posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, anorexia nervosa, bulimia nervosa, obesity, addictions to alcohol, cocaine, heroin, phenobarbital, nicotine or benzodiazepines; cluster headache, migraine, pain, Alzheimer's

disease, obsessive-compulsive disorder, panic disorder, dementia, amnestic disorders, age-related cognitive decline, dementia in Parkinson's disease, neuroleptic-induced parkinsonism, tardive dyskinesias, hyperprolactinaemia, vasospasm, cerebral vasculature vasospasm, cerebellar ataxia, gastrointestinal tract disorders, negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, attention deficit hyperactivity disorder, chronic paroxysmal hemicrania and headache associated with vascular disorders in a mammal, comprising administering an effective amount of a compound according to Claim 1 or a pharmaceutically-acceptable salt thereof effective in treating such disorder or condition and a pharmaceutically-acceptable carrier.

A B T R A C T

Title: NAPHTHAMIDE DERIVATIVES AND THEIR USE

Compounds having the following structure



wherein R^1, R^2, R^3, R^4, m and n are as defined in the specification, in vivo-hydrolysable precursors thereof, pharmaceutically-acceptable salts thereof, the use in therapy and pharmaceutical compositions and methods of treatment using the same.